REMARKS

Status of Claims

Claims 1 and 4-6 are all the claims pending in the application.

Response To Rejection under 35 U.S.C. § 102

Claims 1 and 4-6 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by EP 0583665 ("EP '665"), for the reasons of record. For brevity, these reasons are not reiterated herein.

It appears from the Office Action's assertions, that the rejection is maintained because Applicants have allegedly not shown that the liposome mixture disclosed in EP '665 is different from the presently claimed invention, i.e., "that the benzimidazole in EP ['665] is not associated with the liposome membrane under the incubation conditions."

In addition, it appears the Office Action is asserting that Applicants' arguments of June 27, 2007, are unpersuasive because even though Applicants submitted evidence to show that U.S. Patent Nos. 6,645,522 ("US '522") and 6,348,214 ("US '214"), and WO 97/25560 ("WO '560") fail to guarantee that the process disclosed in EP '665 provides for a liposome that contains the test compound thereof, the Office Action now asserts that Applicants incorrectly directed their comments to US '522, US '214, and WO '560, instead of EP '665.

In response, Applicants submit that EP '665 does not disclose the presently claimed liposomes for at least the following reasons. In addition to the arguments presented June 27, 2007, Applicants submit that EP '665 fails to disclose the presently claimed liposomes, because a mixture of benzimidazole compounds and liposomes in itself, does not result in the presently claimed liposome containing the benzimidazole as a membrane component.

EP '665 merely discloses the separate addition of a benzimidazole compound to an already formed liposome mixture. As disclosed at page 33 of EP '665, the "substances were added [in the following] **order** [emphasis added]: [1)] Test compounds...[dissolved] in DMSO...[2)] Liposome...[3)] ^{3}H-Oleic acid." Because the benzimidazole disclosed in EP '665 is dissolved in a DMSO solution before introduction to the liposome mixture, the addition of the benzimidazole containing solution in step (1) to the preformed liposome mixture of step (2) of EP '665 results in an encapsulation of the benzimidazole within the liposome, and not an incorporation of the benzimidazole into the liposome membrane, as is the case in the presently claimed invention. Thus, EP '665 is different from the presently claimed invention because EP '665 encapsulates, rather than incorporates the benzimidazole compound into the liposome. The benzimidazole solution and preformed liposome mixture of EP '665 are added separately to form a liposome mixture containing encapsulated benzimidazole.

Also, it appears the Office Action acknowledges the separate addition of the benzimidazole to the liposome mixture in EP '665 at page 4, first sentence of the Office Action, stating "[t]he benzimidazole however, is added to the medium containing the liposomes."

In contrast, the presently claimed liposome contains benzimidazole as a membrane component because the benzimidazole compound is combined with the lipid components at the same time, as shown in Example 2 (page 8) of the present specification. Thus, Example 2 of the present specification, and the previous evidence presented in the Amendment of June 27, 2007, shows that certain conditions must be satisfied for a liposome to incorporate the benzimidazole compound, i.e., addition of the benzimidazole and membrane lipids at the same time. EP '665 fails to disclose a liposome produced under these conditions.

Therefore, EP '665 fails to disclose incorporation of a benzimidazole compound into liposomes to prepare liposomes loaded with the benzimidazole compound as a membrane component by combining a benzimidazole compound and lipid components in a mixture for preparation of the liposomes.

Accordingly, reconsideration and withdrawal of the rejection under §102(b) is respectfully requested.

Response To Rejection under 35 U.S.C. § 103

1. EP '665, Aikawa, Kitaguchi, and Schmidt

Claims 1 and 4-6 are rejected under 35 U.S.C. § 103 as allegedly being unpatentable over EP '665 in view of U.S. Patent No. 7,101,532 to Aikawa *et al.* ("Aikawa '532") or U.S. Patent No. 7,008,614 to Kitaguchi *et al.* ("Kitaguchi '614") or U.S. Patent No. 6,077,529 to Schmidt ("Schmidt '529"), for the reasons of record. For brevity, these reasons are not reiterated herein.

In addition, it appears the Office Action is asserting that Applicants' arguments of June 27, 2007, are unpersuasive because, with regard to Aikawa and Kitaguchi, the distinction between the claimed benzimidazole derivative and a contrast compound is not significant because a liposome can encapsulate either the benzimidazole derivate or the contrast compound. With regard to Schmidt, the Office Action asserts that Applicants' arguments that Schmidt teaches asymmetrical liposomes that extract cholesterol are unpersuasive because Aikawa and Kitguchi show that hydrophobic compounds can be encapsulated within the liposomes.

It appears the Office Action is asserting that it would have been obvious for one of ordinary skill in the art to have substituted a hydrophobic contrast compound with the claimed benzimidazole derivative, because both the hydrophobic contrast compound and the claimed benzimidazole derivative are hydrophobic compounds.

In the present case, because EP '665 does not disclose the presently claimed benzimidazole compound as a membrane component, for at least the reasons discussed above, EP '665 fails to render the presently claimed liposomes obvious. To establish a *prima facie* case of obviousness, "the prior art reference (or references when combined) must teach or suggest all the claim limitations." M.P.E.P. §2143. Also, pursuant to M.P.E.P. 2141.02, ascertaining "the differences between the prior art and the claims at issue requires interpreting the claim language, and considering both the invention and the prior art references as a whole." This means that "[i]n determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." Id.

Futher, a *prima facie* case of obviousness may be rebutted by a showing of unpredicted or unexpected results.

In this regard, Applicants note that even if one of ordinary skill in the art was motivated or had reason to substitute a contrast or hydrophobic compound with the claimed benzimidazole compound, the combination of the documents cited by the Office Action would not result in the presently claimed invention. Instead, and as acknowledged by the Office Action, one of ordinary skill in the art would have obtained and expected to obtain "hydrophobic compounds...encapsulated within the liposomes...[and] the encapsulated compound [emphasis added] ...[in the] liposomes to reach the vascular tissue and macrophages" (see page 5, lines 3-7 of Office Action). However, one of ordinary skill in the art would not have obtained, or expected to obtain the superior results obtained by the presently claimed liposomes which contain a benzimidazole compound derivative incorporated as a membrane component.

Applicants submit herewith comparative data, in the attached Rule 132 Declaration of Mr. Kazushiro Aikawa, showing that a benzimidazole compound as a form of the liposome, i.e., incorporated as a membrane component of the liposome, achieves an unexpectedly higher uptake by macrophages in comparison to the uptake by macrophages of the benzimidazole compound that is encapsulated by liposomes[1], i.e., the benzimidazole compound is added separately to a liposome mixture that is not loaded with the benzimidazole as a membrane component and macrophages. As graphically shown in the comparative data, there is no difference between Sample 1 (macrophages + benzimidazole compound) and Sample 2 (Compound I + liposome mixture + macrophages). However, Sample 3 (macrophages + liposome incorporated with Compound 1) shows a significantly higher uptake of macrophage.

As graphically shown in Mr. Aikawa's Declaration, Applicants' claimed liposomes demonstrate an unexpectedly higher uptake of the benzimidazole by macrophages that is superior to the uptake by macrophages of the benzimidazole delivered by the liposomes disclosed in EP '665.

Thus, because the uptake of benzimidazole achieved by Applicants is unexpectedly superior to the uptake of benzimidazole encapsulated by the liposomes disclosed in EP '665, one of ordinary skill in the art would not have obtained or expected to obtain the superior uptake achieved by the presently claimed liposomes from the combination of EP '665, Aikawa, Kitaguchi, and Schmidt.

[1] The liposomes do not contain the benzimidazole incorporated in the liposome membrane, as disclosed in EP '665.

Accordingly, reconsideration and withdrawal of the rejection under § 103(a) is respectfully requested.

2. Aikawa 600, Aikawa, Kitaguchi, and Schmidt

Claims 1 and 4-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,387,600 to Aikawa *et al.* ("Aikawa 600") in view of Aikawa '532 or Kitaguchi '614 or Schmidt '529.

The Office Action asserts that a person of ordinary skill in the art would have incorporated the benzimidazole compounds disclosed in Aikawa '600 into the liposomes disclosed in Aikawa '532, Kitaguchi '614, or Schmidt '529.

Because it appears the Examiner is using Aikawa '600 merely for the disclosure of a benzimidazole compound, the addition of Aikawa '600 would not result in the presently claimed liposomes, for similar reasons discussed above.

Accordingly, reconsideration and withdrawal of this rejection under § 103(a) is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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